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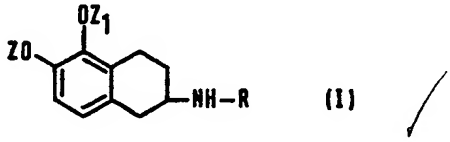
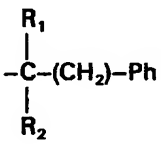
(54) New derivatives of 1,2,3,4-tetrahydronaphthalene, process for their preparation and associated pharmaceutical compositions

(57) 1,2,3,4-tetrahydronaphthalenes are described having the formula:



(I)

where R represents hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 4 to 7 carbon atoms or arylalkyl of the type



where R_1 and R_2, which may or may not be the same, represent hydrogen or C_1–C_4 alkyl;
n = 1 or 2;
Ph represents a phenyl radical possibly having one or more atoms of halogen or hydroxy or methoxy groups or a methylenedioxy group;
Z and Z_1, which may or may not be the same, represent hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 3 to 7 atoms of carbon or an $-AR_3$ radical in which A represents a –CO– or $-SO_2-$ group and R_3 a linear or branched chain alkyl having from 1 to 15 atoms of carbon or a phenyl possibly substituted by a C_1–C_4 alkyl; and their addition salts with pharmaceutically acceptable inorganic or organic acids. These compounds have a sympathomimetic activity.

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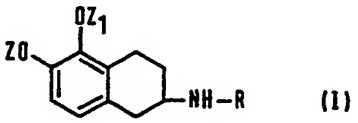
Certain of the chemical formulæ appearing in the printed specification were submitted after the date of filing, the formulæ originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

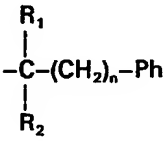
New derivatives of 1,2,3,4-tetrahydronaphthalen , proc ss for th ir preparation and associated pharmaceutical compositions

The invention relates to new derivatives of 1,2,3,4-tetrahydronaphthalene having the general formula:



(I)

where R represents hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 4 to 7 carbon atoms or arylalkyl of the type

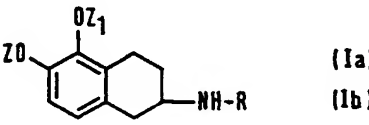


where R_1 and R_2, which may or may not be the same, represent hydrogen or C_1–C_4 alkyl;
n = 1 or 2;
Ph represents a phenyl radical possibly having one or more atoms of halogen or hydroxy or methoxy groups or a methylenedioxy group;
A and Z_1, which may or may not be the same, represent hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 3 to 7 atoms of carbon or an $-AR_3$ radical in which A represents a –CO– or $-SO_2-$ group and R3 a linear or branched chain alkyl having from 1 to 15 atoms of carbon or a phenyl possibly substituted by a C_1–C_4 alkyl; and their addition salts with pharmaceutically acceptable inorganic or organic acids; these compounds have a sympathomimetic activity.

The formula (I) compounds can be present in racemic or diastereoisomeric or optically active form all coming under this invention.

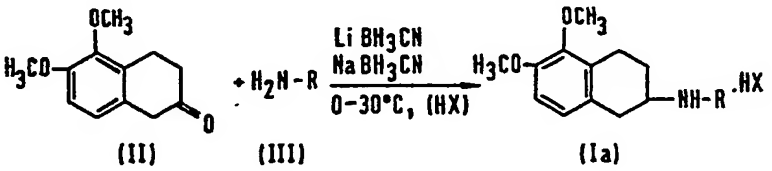
The formula (I) compounds and their salts have appreciable sympathomimetic activity. Because of this property, in the case of a detached agonist activity in comparisons of beta-adrenergic receptors, they may be therapeutically useful for all affections having a spastic component where the main pharmacological action required is relaxation of the smooth muscle tissue by direct action on the beta receptors. As examples of such applications there may be mentioned therapy for bronchial asthma and for broncho-obstructive states in general, relaxation of the smooth muscles of the womb to prevent abortion, relaxation of the urethers in colics and urinary dyskinesia and possible use as coronary dilators. Another possible use is as vasoconstrictors in the case in which an alpha type adrenergic-stimulant activity prevails or as coadjuvants in the treatment of Parkinson's disease in the case of a predominant central dopaminergic activity.

According to this invention the formula (I) compounds can be prepared as will be described hereinafter. A first series of products having the formula Ia and Ib.

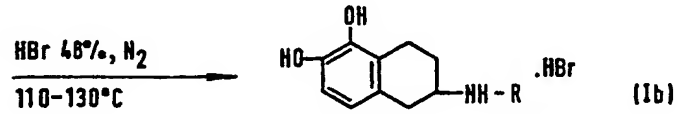


(Ia) Z = Z_1 = CH_3
(Ib) Z = Z_1 = H

where R has the meanings hereinbefore given but Ph does not have methoxy or methylendioxy substituents when Z = Z_1 = H, is prepared by means of the following reaction scheme:



(II) (III) (Ia)



(Ib)

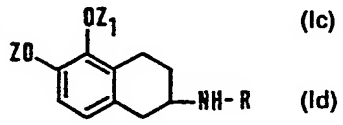
where X is a halogen.

Intermediate (II) (1,2,3,4-tetrahydro-5,6-dimethoxy-2(1H)-naphthalene) is known; see, for instance, Cannon J.G., et al. (J. Med. Chem., 17, 565, 1974) and the primary amines (III) are also known. Condensation between (II) and (III) is carried out at temperatures of from 0 to 30°C in lower C_1–C_5 alcohols or dioxane or acetone which may or may not be aqueous and the simultaneous reduction is performed with sodium or lithium cyanoborohydride.

The resulting compound (Ia) is isolated from the reaction mixture by obvious means and possibly converted into an addition salt with mineral acid, for instance, HCl.

The resulting product (Ia) can possibly be converted, by splitting of the alkoxy group, to the corresponding compound (Ib). To this end, product (Ia) is treated with 48% HBr at temperatures varying from 110 to 130°C for 2 or 3 hours in nitrogen. This leads to optimum yields to the hydrobromide of (Ib) which percipitates cold.

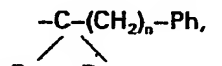
Another series of compounds having the formula Ic and Id



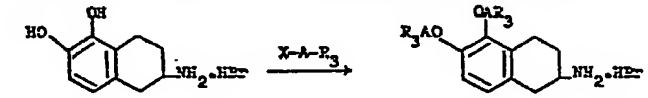
(Ic)

(Id)

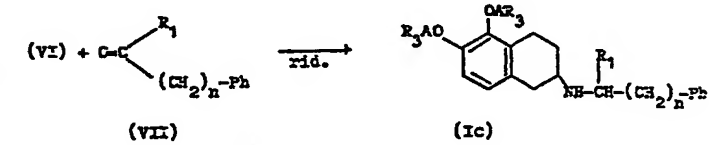
in which (Ic) Z and Z_1 have the meanings already given except as regards hydrogen and alkyls or (Id) $Z = Z_1 = H$, while for R =



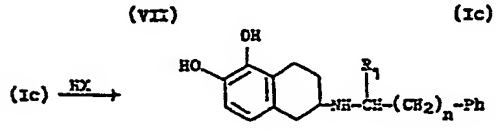
only R_2 represents hydrogen while R_1, *n* and Ph have the meanings hereinbefore given, is prepared by means of the following reaction scheme:



(IV) (V) (VI)



(VII) (Ic)



(Id)

wh re X r presents halogen while A, n, R_1, R_3 and Ph have the meanings previously given except that R_1 must be other than hydrogen.

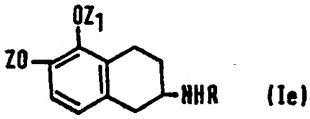
This method is particularly useful wh n the chain bonded to the nitrogen contains a phenyl

radical substituted with methoxy or methylenedioxy which ar requir d to remain unchanged. Compound (IV), which can b prepared by the method previously described, is acylat d with reagents X–A–R_3 (chlorides of aliphatic or aromatic carboxylic acids or aliphatic or aromatic sulfochlorides) with the use as solvent of trifluoroacetic acid to prevent possible reactions of the amine function at temp ratures of from 30 to 80°C for approximately 1 hour, whereafter the reaction mixture is evaporated dry and the intermediates (VI) are isolated from the residue with very high yields.

The intermediates (VI) are then reacted with the ketones (VII) in the presence of alkaline cyanoborohydrides in conditions very similar to those described for preparing compounds (Ia).

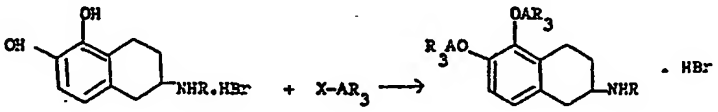
The resulting products (Ic) can be converted into the corresponding formula (Id) compounds by acid hydrolysis (preferably with HCl) in an appropriate solvent at temperatures of from 10 to 70°C. It is often convenient to perform continuous azeotropic distillation of the reaction mixutre to shift the reaction equilibrium completely towards the required product (Id). The reaction usually takes from 4 to 7 hours to complete.

Compounds having the formula (Ie)



(Ie)

in which $Z = Z_1 = AR_3$ while R has the meanings given for the general formula (I) but is always other than hydrogen and does not contain phenols having any degree of substitution, X, A, and R_3 having the meanings hereinbefore given, can be prepared by means of the reaction:



(VIII) (V) (Ie)

The starting product (VIII) can readily be prepared with the method described for the preparation of formula (Ib) compounds, and the reaction leading to the formula (Ie) end products is completely similar to the reaction described for preparing formula (VI) intermediates, more particularly as regards the use of CF_3COOH. The yields of this reaction are very high and always greater than 95%.

The formula (I) compounds thus prepared can also form addition salts with pharmaceutically acceptable acids, for instance, inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric or hydrobromic acid or organic acids such as oxalic, maleic, fumaric, malic, tartaric, citric and ascorbic acid.

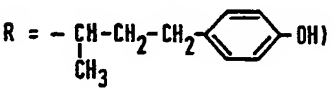
These salts can readily be prepared in known manner, for instance, by an addition of an equimolar quantity or an excess of acid to a compound (I) solution in a solvent consisting of lower alcohols, acetone or the like.

The invention is described in greater detail in the following purely non-limitative examples.

EXAMPLE 1

5,6-dimethoxy-2(4-p-hydroxyphenyl-2-butyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (IX)

(formula Ia with



28 g (0.135 mol) of intermediate product (II) and 300 ml of methanol are introduced into a 500 ml reaction flask. A solution prepared from 11 g (0.045 mol) of 4(p-hydroxyphenyl)-2-amino-butane hydrobromid , 125 ml m thanol and sufficient 5% methanal potash bring the pH to 7–7.2 is dripped slowly into the solution in the r action vessel in a reduced flow of nitrogen. The temperature is maintain d at 8°C during dripping and th mixtur is agitat d. Upon th completions of dripping 11 g of $NaBH_3CN$ are introduced slowly cold, whereafter th mixture is allowed to react at ambient t mperature for 20 hours, whereafter the mixture is acidified with conc. HCl and the solv nt evaporated. The residue is washed in ether, dissociated in water, brought to a pH of 10 with 10% KOH and extracted with chloroform. The chloroform phase is washed in water and dried on Na_2SO_4 and th r sidue is vaporated and precipitated with

etheric hydrochloric acid. It is recrystallised (decolouring with carbon) in absolute ethyl alcohol. 12.4 g of a white crystalline product (yield of 70.8%) having a melting point of from 255 to 257°C are yielded.

Spectrum ^1H–NMR at 60 MHz (DMSO d_6) (ppm, δ) = 9.3 (s, broad, 2H exchanges with $D_2O = {}^+NH_2$); 9.1 (s, 1H exchanges with D_2O, OH); 7,1–6,6 (m, 6H aromatics); 3.8 (s, 3H = OCH_3); 3.7 (s, 3H = $^-OCH_3$); 3.5–1.7 /m, 12H (CH and CH_2 of cyclohexane)/; 1.4 (/d, (J – 5CpS), 3H, CH_3/.

Elementary analysis: for $C_{22}H_{30}ClNO_3$

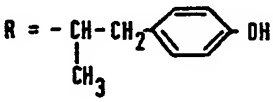
Calculated %C = 67.42; H = 7.72; N = 3.57

Found %C = 67.22; H = 7.57; N = 3.71.

The following compounds are prepared similarly:

5,6-dimethoxy-2-(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (X)

(formula Ia with



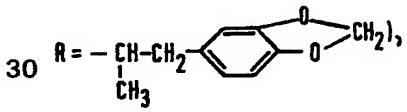
m.p. 238–240°C, NMR spectrum in agreement.

Elementary analysis: for $C_{21}H_{28}ClNO_3$

Calculated %C = 66.74; H = 7.47; N = 3.71

Found %C = 66.67; H = 7.30; N = 3.79;

5,6-dimethoxy-2-/3-(3′,4′-methylenedioxyphenyl)-2-propyl/amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XI), (formula Ia, with



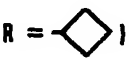
m.p. 270–271°C, NMR spectrum in agreement.

Elementary analysis: for $C_{22}H_{28}ClNO_4$

Calculated %C = 65.09; H = 6.95; N = 3.45

Found %C = 64.93; H = 6.86; N = 3.59;

5,6-dimethoxy-2-cyclobutylamino-1,2,3,4-tetrahydronaphthalene hydrochloride (XIII) (formula Ia, with

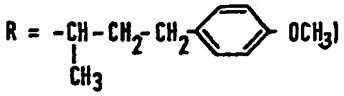


m.p. 204–207°C, NMR spectrum in agreement.

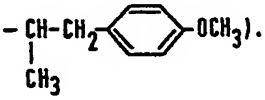
5,6-dimethoxy-2-(p-hydroxycyclohexyl)-amino-1,2,3,4-tetrahydronaphthalene (XIII) (formula Ia with

m.p. >240°C (decomposition), NMR spectrum in agreement.

5,6-dimethoxy-2(4-p-methoxyphenyl-2-butyl)-amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XIV) (formula Ia with

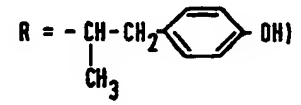


5,6-dimethoxy-2-(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XV) (formula Ia, with R =



EXAMPLE 2

5,6-dihydroxy-2-(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrobromide (XVI) (formula Ib, with



9.4 g, corresponding to 0.025 mol, of the compound (X) prepared by the method of Example 1 and 115 ml of 48% HBr are introduced into a 200 ml reactor. The mixture is heated with agitation and in a light flow of nitrogen to a temperature of 110°C and maintained thereat for 3 hours. After cooling of the reaction mixture to 0°C, the precipitated product is filtered, dried and recrystallised from acetonitrile, 8.1 g, or a yield of 82%, are obtained of a whitish-grey product which has a melting point of 246–248°C and whose characteristics are as follows:

Spectrum ^{1}H–NMR at 60 MHz (DMSO d_6) (ppm, δ) = 9.1 (s, broad, 2H exchanges with D_2O = $^+NH_2$); 7.3–6.5 (m, 6H, aromatics); 3.9 (s, broad, 3H exchanges with D_2O = 3OH, phenolics); 3.7–1.7 /m 10 H (CH and CH_2 of cyclohexane)/; 1.35 /d, (J = 6 cps), 3H, CH_3/.

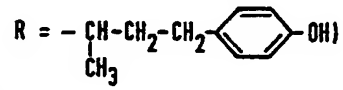
Elementary analysis: for $C_{19}H_{24}BrNO_3$

Calculated %C = 57.87; H = 6.13; N = 3.55

Found %C = 57.73; H = 5.97; N = 3.70.

The following compounds can be prepared similarly from the corresponding methoxylated derivatives in position 5 and 6:

5,6-dihydroxy-2-(4-p-hydroxyphenyl-2-butyl)amino-1,2,3,4-tetrahydronaphthalene hydrobromide (XVII) (formula Ib, with



m.p. 240–242°C.

Spectrum ^{1}H–NMR at 60 MHz (DMSO d_6) (ppm, δ) = 9.2–8.6 (s, broad, 5H = $^+NH_2$ + 3OH phenolics, exchanges with D_2O): 7.1–6.3 (m, 6H, aromatics); 3.7–1.7 /m, 12H (CH + CH_2 of cyclohexane)/; 1.35 /d, (J≃6 cps), 3H CH_3/.

Elementary analysis: for $C_{20}H_{26}BrNO_3$

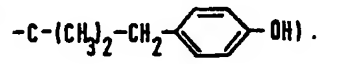
Calculated %C = 58.83; H = 6.42; N = 3.43

Found %C = 58.68; H = 6.29; N = 3.54;

5,6-dihydroxy-2-ter-butylamino-1,2,3,4-tetrahydronaphthalene hydrobromide (XVIII) (formula Ib, with R = $C(CH_3)_3$);

5,6-dihydroxy-2-cyclobutylamino-1,2,3,4-tetrahydronaphthalene hydrobromide (XIX) (formula Ib, with R = cyclobutyl);

5,6-dihydroxy-2/2-p-hydroxyphenyl-1,1-dimethylether/amino-1,2,3,4-tetrahydronaphthalene hydrobromide (XX) (formula Ib, with R =



EXAMPLE 3

(a) *5,6-dipivaloyloxy-2-amino-1,2,3,4-tetrahydronaphthalene.HBr (XXI)*

(formula VI with $R_3A = (CH_3)_3C–CO$)

11.2 g (0.0437 mol) of 5,6-dihydroxy-2-amino-1,2,3,4-tetrahydronaphthalene hydrobromide prepared as in Example 2 are suspended in 29 ml of CF_3COOH and 18.5 g of pivaloyl chloride is dripped into the mixture over a period of 15 minutes. The mixture is then heated to 80°C for 1 hour (HCl is evolved). After cooling the mixture is evaporated until a viscous oil is obtained which is taken up with ethyl ether and petroleum ether. A white crystalline product precipitates, is filtered and washed in petroleum ether. 15.7 g (84% yield) of the required product are obtained; m.p. 256–258°C.

Spectrum ^{1}H–NMR at 60 MHz (DMSO d_6)

(ppm, δ) = 8.4 (s, broad, 3H, exchang s with D_2O $^+NH_3$); 7.0 /s, (unr solved), 2H aromatics/; 2.5–1.8 /m, 7H, (CH and CH_2 of cyclohexane)/; 1.35 (s, 9H, $–CO–C(CH_3)_3$); 1.30 (s, 9H, $CO–C(CH_3)_3$).

Elementary analysis: for $C_{20}H_{30}BrNO_4$

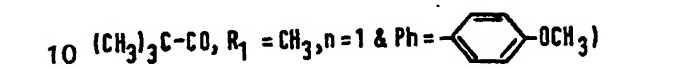
Calculated %C = 56.07; H = 7.06; N = 3.27

Found %C = 55.92; H = 6.94; N = 3.40.

5,6-diisobutirroyloxy-2-amino-1,2,3,4-tetrahydronaphthalene hydrobromide (XXII) (formula VI,

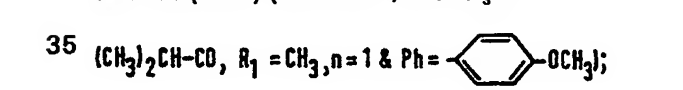
with $R_3A = (CH_3)_2CH-CO$), m.p. 168–170°C, NMR spectrum in agreement with the proposed structur , is prepared similarly.
Elementary analysis: for $C_{18}H_{26}BrNO_4$
Calculat d %C = 54.00; H = 6.55; N = 3.50
Found %C = 53.87; H = 6.41; N = 3.66.

(b) *5,6-dipivaloyloxy-2-(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride* (XXIII) (formula Ic, with $R_3A =$

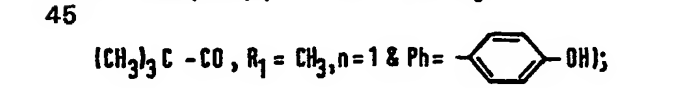


8.3 g (0.05 mol) of p-methoxybenzyl-methyl-ketone dissolved in 100 ml of methanol are introduced into a 250 ml reaction vessel. A solution of 7.7 g (0.02 mol) of 5,6-dipivaloyloxy-2-amino-1,2,3,4-tetrahydronaphthalene hydrobromide (Example 3*a*) in 54 ml of methanol (+ 5% methanoic KOH sufficient to bring the pH to 7–7.5) is dripped into the solution at from 4 to 8°C. Upon the completion of dripping the mixture is agitated for 30 minutes, whereafter 3.4 g of $LiBH_3CN$ is introduced slowly at a temperature of from 5 to 9°C. The mixture is left to react at ambient temperature for 20 hours, then acidified with conc. HCl, and the solvent is evaporated. The residue is first washed in ethyl ether, then dissolved in water, brought to a pH of 9–9.5 with 10% KOH and extracted with $CHCl_3$. The chloroform phase is washed in water, dried on Na_2SO_4 and completely evaporated. The residual oil is precipitated with etheric HCl; the precipitate is filtered, washed in ether and recrystallised from absolute ethanol/ethyl ether. 6.5 g (61% yield) of a white crystalline product with a melting point of 224–226°C are obtained.
Spectrum ^1H–NMR at 60 MHz (DMSO d_6)
(ppm, δ) = 7.3–6.8 (m, 6H, aromatics); 4.5 (s, 2H, exchanges with D_2O $^+NH_2$); 3.7 (s, $-O-CH_3$); 3.5–1.9 /m, 10 H(CH + CH_2 of cyclohexane)/; 1.4 /d, (J≃7cps), 3H, $=CH_3$/; 1.3 (s, 9H $-CO-C(CH_3)_3$); 1.25 (s, 9H, $CO-C(CH_3)_3$).
Elementary analysis: for $C_{30}H_{42}ClNO_5$
Calculated %C = 67.71; H = 7.77; N = 2.63
Found %C = 67.55; H = 7.63; N = 2.74

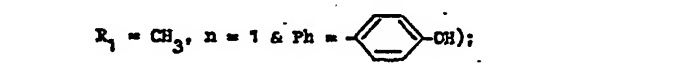
The following compounds can be prepared similarly:
5,6-diisobutirroyl-2-(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXIV) (formula Ic, with $R_3A =$



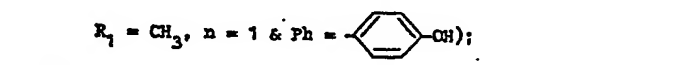
m.p. 245–247°C;
NMR spectrum: in agreement with the structure.
Elementary analysis: for $C_{28}H_{38}ClNO_5$
Calculated %C = 66.72; H = 7.60; N = 2.78
Found %C = 66.50; H = 7.46; N = 2.92;
5,6-dipivaloyloxy-2-(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXV) (formula Ic, with $R_3A =$



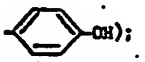
5,6-di-p-toluene-sulphonyloxy-2(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXVI) (formula Ic, with R_3A = p-toluenesulphonyl,



5,6-di-p-toluyloxy-2(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXVII) (formula Ic, with R_3A = p-methylbenzoyl,

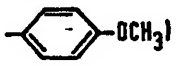


5,6-dibenzoyloxy-2(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXVIII) (formula Ic, with R_3A = benzoyl,

$R_1 = CH_3$, $n = 1$ & Ph =  ;

EXAMPLE 4

5,6-dihydroxy-2(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXIX) (formula Id, with $R_1 = CH_3$, $n = 1$

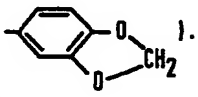
Ph =  ,

3 g (0.056 mol) of 5,6-dipivaloyloxy-2(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene hydrochloride, then a 100 ml of methanol, then, with agitation, 50 ml of 35% aqueous HCl are introduced into a 500 ml reaction vessel. The mixture is reacted at 60°C for 3 hours, then evaporated to a reduced volume, whereafter the inputs of methanol and hydrochloric acid are repeated. Repeating the operation two or three times leads to complete reaction of the product (chromatographic check). The product is isolated after evaporation of the reaction mixture and recrystallization from acetonitrile. 1.5 g of a creamy white crystalline powder (73% yield), with a melting point of 232–234°C, are obtained.

Spectrum ^{1}H–NMR at 60 MHz (DMSO d_6)
(ppm δ) = 9.0 (s, wide, 2H, exchanges with D_2O: $^+NH_2$); 7.3–6.4 (m, 6H, aromatics); 4.1 (s, 2H, exchanges with D_2O: OH phenolics); 3.75 (s, 3H = –O–CH_3); 3.6–1.9 /m, 10H (CH + CH_2 of cyclohexane)/; 1.3 /d, (J≃4cps), 3H, CH_3/.

Elementary analysis: for $C_{20}H_{26}ClNO_3$
Calculated %C = 66.01; H = 7.20; N = 3.85
Found %C = 65.87; H = 7.12; N = 3.82

5,6-dihydroxy-2/3-(3′,4′-methylenedioxyphenyl)-2-propyl/amino-1,2,3,4-tetrahydronaphthalene hydrochloride (XXX) (formula Id, with

$R_1 = CH_3$, $n = 1$ & Ph =  .

can be prepared similarly.

EXAMPLE 5

5,6-dipivaloyloxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrobromide (XXXI) (formula Ie with $Z = Z_1 = (CH_3)_3C–CO$ and $R = CH_3$).

3 g (0.011 mol) of 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydronaphthanlene hydrochloride prepared by the method of Example 2 are placed in a 50 ml flask and suspended in 7.5 ml of CF_3COOH. 4.5 g of pivaloyl chloride are then dripped in with agitation and upon the termination of dripping the mixture is heated at 80°C for 1 hour. The reaction mixture is allowed to cool, then evaporated until dry, then taken up in ethyl ether, there being obtained by cold precipitation a white crystalline product which is filtered and washed in ethyl ether—4.7 g (98% yield) of a white crystalline powder with a melting point of 220–222°C.

Spectrum ^{1}H–NMR at 60 MHz (DMSO d_6)
(ppm δ) = 8.7 (s, 2H, exchanges with $D_2\theta$: $^+NH_2$); 6.8–6.2 (m, 2H aromatics); 3.4 (s, 3H, $^+N–CH_3$); 3.2–1.9 (m, 7H, cyclohexanic hydrogens); 1.35 /s, 9H, –CO–$C(CH_3)_3$/; 1.30 /s, 9H, –CO–$C(CH_3)_3$/.

Elementary analys: for $C_{21}H_{32}BrNO_4$
Calculated %C = 57.00; H = 7.29; N = 3.17
Found %C = 56.82; H = 7.16; N = 3.25.

The following compound can be prepared similarly:
5,6-diisobutyrroyloxy-2-methylamino-1,2,3,4-tetrahydronaphthalene hydrobromide (XXXII) (formula Ie, with $Z = Z_1 = (CH_3)_2CH–CO$) and $R = CH_3$);
m.p. 176–178°C; NMR and elementary analysis in agreement; *5,6-diisobutirroyloxy-2-isopropylamino-1,2,3,4-tetrahydronaphthalene hydrobromide* (XXXIII) (formula Ie, with $Z = Z_1 =$ (-$CH_3)_2CH–CO$ and R = isopropyl); m.p. 214–216°C;
NMR and elementary analysis in agreement;
5,6-dipivaloyloxy-2-isopropylamino-1,2,3,4-tetrahydronaphthalene hydrobromide (XXXIV) (formula Ie, with $Z = Z_1 = (CH_3)_3C–CO$ and R = isopropyl); m.p. 230–234°C; NMR and lementary analysis in agr ement.

The formula (I) compounds and th ir salts have been shown in laboratory tests on animals to hav interesting pharmacodynamic properties. Single administration toxicity tests were made on male rats of the strain Crl: CD–1(ICR)BR. Compounds IX, X and XVII given intraveneously were

found to be non-toxic up to the limit of solubility in a dose range of from 3 to 20 mg/kg.

The results given in Tabl 1 were obtained with compound XVI.

TABLE 1

Compound	Method of administration	LD_{50} (mg/kg)
XVI	i.v.	54 (58–50)
	p.o.	1020 (1106–941)

The stimulus which some of the compounds having the general formula (I) have on the beta-2 adrenergic receptors was tested as a bronchodilatory activity in comparisons of the bronchospasm induced by acetylcholine and hystamine in the anesthetized guinea pig.

The tests were carried out on white male guinea pigs (Dunkin-Hartley strain) along the lines described by Konzett and Rossler (Arch. Exp. Pathol. Pharmakol. 195, 71, 1940). Drugs known to have a strong bronchodilatory action were used as controls. The compounds being studied were given intraveneously.

Compound XVI proved to be particularly active in these studies, exhibiting a bronchodilatory activity only a little less than that of isoproterenol and appreciably greater than that of salbutmaol, salmephamol and clenbuterol.

The results expressed as percentage inhibitions of bronchospasms are given in Table 2 as doses providing a 50% inhibition of maximum response and determined by the dose-response curves (ID_{50}).

TABLE 2

Compound	ID_{50} (nmol/kg) Bronchospasm induced by: Hystamine	Acetylcholine
XVII		90
XVI	1.6	3.4
Isoproterenol	0.45	1.25
Salbutamol	4.3	13.0
Salmethamol	9.5	15.0
Clenbuterol	25.0	26.0

Compound XVI also proved to be effective on acetylcholine-introduced bronchospasm in the guinea pig even after an intra-tracheal administration in the form of micronised powder.

Compounds X and XXIX were also found to have an appreciable antibronchospastic activity; when given intraveneously in a dose of 3 μmol/kg they produced a percentage inhibition of the acetylcholine-induced bronchospasm in the guinea pig of 92.8% and 82.6% respectively.

The selectivity of these compounds for the beta-2 adrenergic receptors as compared with the β_1 cardiac receptors was shown by testing *in vitro* their chronotropic and inotropic activity on a heart preparation isolated from a perfused rabbit (male white rabbits of New Zealand strain), isoproterenol being used in all cases as the control. In these tests compound X proved to have only a reduced chronotropic activity; compounds XVI and XVII had only some chronotropic and inotropic activity and in any case much below that of isoproterenol which produced substantial alterations of all the cardiac parameters considered. By way of example the values of the modifications produced by these products on the heart beat rate at a dose of 0.3 nmol/kg, expressed in beats/minute as a difference between the increment and the basic value, are given in Table 3.

TABLE 3

Compound	Average values ± ES
XVII	12.0 ± 8.3
XVI	4.0 ± 2.3
Isoproterenol	108.3 ± 13.2

A point of particular interest is that the activity of compound XVI was confirmed; while producing a bronchodilatory effect only slightly less intense than that of isoproterenol but with much reduced cardiac effects. It thus proves that it has a specific action on the beta-2 adrenergic receptors.

This specificity was further assessed in preparations isolated from the trachea and atria of the guineapig, in all cases in comparison with isoproterenol, than which compound XVI is 23 times more selective.

The results of these tests are given in Table 4.

TABLE 4

Average values of pD_2 (within limits of reliability), α (± ES) and the index of relative β_2 selectivity obtained in preparations isolated from the trachea and atria of guinea pigs as a result of administering the compounds mentioned

	Isolated trachea		Isolated atria		
Compound	β_2 affinity pD_2 (T)	Intrinsic β_2 activity (T)	β_1 affinity pD_2 (A)	Intrinsic β_1 activity α (A)	Index of relative β_2 selectivity (affinity)
Isoproterenol	8.40 (8.31–8.49)	1.00	9.09 (9.02–9.16)	1.00	1.00
XVI	7.76 (7.67–7.86)	0.99 ± 0.006	7.02 (6.96–7.22)	0.54 ± 0.06	23.0

In the tests of inhibiting acetylcholorine-induced bronchospasms by the methods of Konzett and Rossler, interesting results were also obtained with other compounds having the general formula (I) which, although having a less intense effect, have tha advantage of a much longer duration of the anti-bronchospastic activity than the control drug (isoproterenol) (Table 5).

TABLE 5—Percentage inhibition of acetylcholine-induced bronchospasms at different periods of time from the intraveneous administration of the compounds being studied—average values ± ES.

Compound and dosage	Minutes after administration 1	6	11	16	21	26	31	36	41
XXXI (1 µmol/kg)	14,3 ± 3,0	51,7 ± 4,1	53,5 ± 3,6	46,3 ± 2,2	43,6 ± 1,8	40,3 ± 3,3	36,8 ± 2,2	33,0 ± 3,0	30,4 ± 3,6
XXXII (0,3 µmol/kg)	73,6 ± 7,1	59,8 ± 5,8	46,3 ± 5,6	29,9 ± 4,1	23,6 ± 4,6	18,8 ± 4,6	12,9 ± 4,0	11,2 ± 3,8	9,8 ± 3,4
XXXIII (1 µmol/kg)	63,4 ± 11,0	31,3 ± 2,0	18,7 ± 6,1	13,9 ± 7,0	10,9 ± 5,6	9,2 ± 4,8	4,7 ± 4,0	3,1 ± 3,1	1,1 ± 1,1
Isoproterenol (0,03 µmol/kg)	92,4 ± 2,0	22,1 ± 11,1	5,8 ± 5,8	2,4 ± 2,4	0				

Some appreciable results were obtained with the compounds according to this invention in other tests for other kinds of activity. In the d termination of *diuretic activity* compound XXXII when given intraperitoneally produced in th rat up t 1 hour from treatment an approximately 10-fold increase in the quantity f urine excreted, measured in ml. In the determinati n f *renal* vasocilatory activity, as t sted on the isolat d renal artery of the rabbit, compound XXI produced a marked dose-dependent dilation of 50 and 5 times th intensity of dopamine and isoproterenol respectively, the substances used as controls.

This invention also r lates to all th industrially us ful aspects relating to the us of

compounds (I) or their addition salts with acceptable pharmaceutical acids as bronchodilators or utero-relating agents in th case of sp cific agonist action in the comparisons of the beta-2 adrenergic receptors, as vasoconstrictors in states of hypotension, shock, bleeding from small surface vessels, congestion of the mucosae (allergic forms of rhinitis, sinusitis etc), in the case of predominant alpha activity or as coadjuvants in th tr atm nt of Parkinson's dis ase in the case of dopaminergic central action.

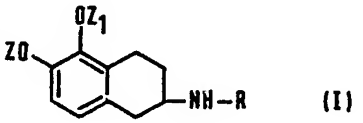
An important aspect of the invention therefore consists of pharmaceutical formulations containing predetermined quantities of formula (I) compounds or their salts. The compounds according to the invention can be given orally, rectally, subcutaneously, inhalatorially or topically according to the kind of use, for instance, in the form of tablets, capsules, suppositories, injection flasks, dosed sprays, ointments, pomades and creams, all these formulations containing in addition to the active principle the solvents, excipients, auxiliaries, etc. conventional in the pharmaceutical art.

For instance, pharmaceutical formulations of an anti-bronchospastic substance to be given orally in the form of capsules or tablets can contain as active principle compound XVI in unit dose of from 0.5 to 5 mg, preferably from 2 to 2.5 mg.

Pharmaceutical formulations of an antibronchospastic substance to be given by inhalation in the form of a dosed aerosol can contain as active principle compound XVI in unit concentrations of from 0.1 to 1.5 mg, preferably of from 0.5 to 1 mg.

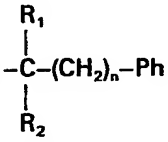
CLAIMS

1. As new compounds, derivaties of 1,2,3,4-tetrahydronaphthalene having the formula (I)



(I)

where R represents hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 4 to 7 carbon atoms or arylalkyl of the type



where R_1 and R_2, which may or may not be the same, represent hydrogen or C_1–C_4 alkyl;
n = 1 or 2;
Ph represents a phenyl radical possibly having one or more atoms of halogen or hydroxy or methoxy groups or a methylenedioxy group;
Z and Z_1, which may or may not be the same, represent hydrogen, C_1–C_4 alkyl, cycloalkyl containing from 3 to 7 atoms of carbon or an $-AR_3$ radical in which A represents a –CO– or $-SO_2-$ group and R_3 a linear or branched chain alkyl having from 1 to 15 atoms of carbon or a phenyl possibly substituted by a C_1–C_4 alkyl; and their addition salts with pharmaceutically acceptable inorganic or organic acids.

2. Compounds according to claim 1, characterised in that in formula (I):
R represents hydrogen, methyl, isopropyl, t.butyl, cyclobutyl, 3-p-hydroxyphenyl-2-propyl, 3-p-methoxyphenyl-2-propyl, 3-(3′,4′-methylenedioxyphenyl)-2-propyl, 2-p-hydroxyphenyl-1,1-dimethylethyl, 4-p-hydroxyphenyl-2-butyl, 4-p-methoxyphenyl-2-butyl, 4-(3′,4′-methylenedioxyphenyl)-2-butyl;
Z and Z_1 are equal and represent hydrogen, methyl, pivaloyl, isobutirroyl, benzoyl, p-toluyl, p-toluensulfonyl.

3. As compound according to claim 2, 5,6-dimethoxy-2(4-p-hydroxyphenyl-2-butyl)amino-1,2,3,4-tetrahydronaphthalene.

4. As compound according to claim 2, 5,6-dimethoxy-2-(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

5. As compound according to claim 2, 5,6-dimethoxy-2-/3-(3′,4′-methylenedioxyphenyl)-2-propyl/-amino-1,2,3,4-tetrahydronaphthalene.

6. As compound according to claim 2, 5,6-dimethoxy-2-cyclobutylamino-1,2,3,4-tetrahydronaphthalene.

7. As compound acc rding to claim 2, 5,6-dimethoxy-2-(p-hydroxycyclophexyl)-amino-1,2,3,4-tetrahydronaphthalene.

8. As compound according to claim 2, 5,6-dimethoxy-2(4-p-methoxyph nyl-2-butyl)amino-

1,2,3,4-t trahydronaphthalen .

9. As compound acc rding to claim 2, 5,6-dim thoxy-2-(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalen .

10. As compound according to claim 2, 5,6-dihydroxy-2-(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

11. As compound according to claim 2, 5,6-dihydroxy-2-ter-butylamino-1,2,3,4-tetrahdronaphthalene.

12. As compound according to claim 2, 5,6-dihydroxy-2-cyclobutylamino-1,2,3,4-tetrahydronaphthalene.

13. As compound according to claim 2, 5,6-dihydroxy-2-/2-p-hydroxyphenyl-1,1-dimethylethyl/amino-1,2,3,4-tetrahydronaphthalene.

14. As compound according to claim 2, 5,6-dipivaloyloxy-2-amino-1,2,3,4-tetrahydronaphthalene.

15. As compound according to claim 2, 5,6-diisobutyroyloxy-2-amino-1,2,3,4-tetrahydronaphthalene.

16. As compound according to claim 2, 5,6-dipivaloyloxy-2(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

17. As compound according to claim 2, 5,6-dipivaloyloxy-2(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

18. As compound according to claim 2, 5,6-di-p-toluenesulfonyloxy-2(3-p-hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

19. As compound according to claim 2, 5,6-diisobutirroyl-2(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

20. As compound according to claim 2, 5,6-di-p-toluyloxy-2(3-p.hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

21. As compound according to claim 2, 5,6-dibenzoyloxy-2(3-p.hydroxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

22. As compound according to claim 2, 5,6-dihydroxy-2(3-p-methoxyphenyl-2-propyl)amino-1,2,3,4-tetrahydronaphthalene.

23. As compound according to claim 2, 5,6-dihydroxy-2/3-(3′,4′-methylenedioxyphenyl)-2-propyl/amino-1,2,3,4-tetrahydronaphthalene.

24. As compound according to claim 2, 5,6-dipivaloyloxy-2-methylamino-1,2,3,4-tetrahydronaphthalene.

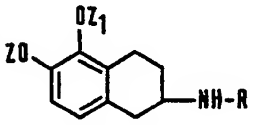
25. As compound according to claim 2, 5,6-diisobutirroyloxy-2-methylamino-1,2,3,4-tetrahydronaphthalene.

26. As compound according to claim 2, 5,6-diisobutirroyloxy-2-isopropylamino-1,2,3,40tetrahydronaphthalene.

27. As compound according to claim 2, 5,6-dipivaloyloxy-2-isopropylamino-1,2,3,4-tetrahydronaphthalene.

28. Compounds according to claims 1–25, characterised in that they occur in the racemic, diastereoisomeric or optically active form.

29. A process for the preparation of the formula (Ia) and (Ib) compounds

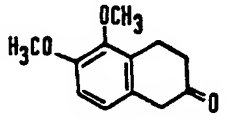


(Ia) $Z = Z_1 = CH_3$

(Ib) $Z = Z_1 = H$

in which R has the meanings specified in claims 1 and 2 but Ph does not contain methoxy or methylenedioxy substituents when $Z = Z_1 = H$, characterised in that:

(a) The compound of formula II:



(II)

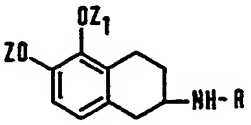
is condensed with a primary amine of the $H_2N–R$ (III) kind in which R takes on the meanings hereinbefor specified, with simultan ous r duction and subsequent isolation of the resulting formula (Ia) compounds;

(b) The resulting (Ia) ompounds may b given a furth r reacti n to split the alkoxy groups, with conversion of the corresponding formula (Ib) compounds.

30. A process according to claim 27, characterised in that th condensation reaction between compounds (II) and (III) takes plac at t mperatures of from 0 to 30°C, reduction is

performed with the use of alkaline cyanoborohydrides and the subsequent alkoxy group splitting reaction is performed with 48% aqueous hydrobromic acid at temperatures of from 110 to 130°C in a nitrogen flow for 2 or 3 hours.

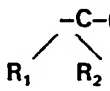
31. A process for the preparation of compounds having the formula (Ic) and (Id):



(Ic)

(Id)

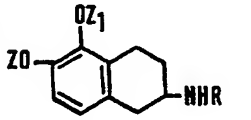
in which (Ic) Z and Z_1 have the meanings specified except in the case of hydrogen and alkyls or (Id) $Z = Z_1 = H$ while, for



only R_2 represent hydrogen or R_1, *n* and Ph have the meanings given, characterised in that:
(a) the phenolic hydroxies of 5,6-dihydroxy-2-amino-1,2,3,4-tetrahydronaphthalene are acylated with acyl chlorides having the formula R_3A–Cl in which R_3 and A have the meanings hereinbefore given;
(b) the resulting intermediates are reacted in reducing amination conditions with ketones having the formula R_1–CO–$(CH_2)_n$–Ph in which *n* and Ph have the meanings already given and R_1 is other than hydrogen;
(c) the resulting formula (Ic) products thus obtained may be given acid hydrolysis for conversion to the corresponding derivatives (Id).

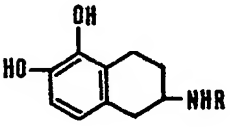
32. A process according to claim 29, characterised in that acylation takes place in the presence of trifluouroacetic acid at a temperature of from 30 to 80°C, the reducing amination reaction is carried out with alkaline cycanborohydrides and the subsequent acid hydrolysis reaction is carried out with hydrochloric acid in the presence of an appropriate solvent at temperatures varying between 10 and 70°C.

33. A process for the preparation of compounds having the formula (Ie):



(Ie)

in which $Z = Z_1 = AR_3$ (where R_3 has the meanings already given) while R has the meanings already given but is always other than hydrogen and does not contain phenols, characterised in that derivatives having the formula (VIII)



(VIII)

in which R has the meanings given in this claim, are reacted with acyl chlorides having the formula R_3A–Cl whereafter the resulting formula (Ie) compounds are isolated.

34. A process according to claim 31, characterised in that the reaction is carried out in the presence of trifluoroacetic acid at temperatures of from 30 to 80°C.

35. A pharmaceutical formulation having a bronchodilatory, utero-relaxing, vasoconstrictive or anti-parkinsonian activity and having as active principle at least one compound according to claims 1 to 26.

36. A pharmaceutical formulation according to claim 33 for oral, rectal, subcutaneous, inhalatory or topical administration in the form of capsules, possibly coated pills, suppositories, phials, controlled spray, solution for inhalation, cream or gel.

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